Different forms of iron accumulation in the liver on MRI

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ABSTRACT
Magnetic resonance imaging (MRI) is a well-established imaging modality to evaluate increased iron deposition in the liver. Both standard liver imaging series with in-phase and out-of-phase T1-weighted sequences for visual detection, as well as advanced T2- and T2*-weighted measurements may be used for mapping the iron concentration. In this article, we describe different forms of liver iron accumulation (diffuse, heterogeneous, multinodular, focal, segmental, intralesional, periportal, and lobar) and hepatic iron sparing (focal geographic and nodular). Focal iron sparing is characterized by hypointense areas on R2* map and hyperintense areas on T2* map. We also illustrate MRI findings of simultaneous hepatic iron and fat accumulation. Coexistence of iron (siderosis) and fat (steatosis) can make interpretation of in- and out-of-phase T1-weighted images difficult; calculation of proton density fat fraction and R2* maps can characterize abnormal signal changes observed on in- and out-of-phase images. Knowledge of different forms of hepatic iron overload and iron sparing and evaluation of T2* and R2* maps would allow correct diagnosis of iron-associated liver pathologies.

Magnetic resonance imaging (MRI) findings of iron overload, particularly in the liver, are well established (1). Hepatic iron overload is abnormal accumulation of iron in hepatocytes, Kupffer cells, or both (2, 3). Hepatic iron overload is commonly associated with hereditary hemochromatosis, transfusion-related iron overload, and chronic hepatopathies (4). MRI is mainly preferred for detection of hepatic iron. However, different forms of iron accumulation and iron sparing can make interpretation of images difficult. Knowledge of different forms of hepatic iron overload and iron sparing, and evaluation of T2* and R2* maps would allow correct diagnosis of iron-associated liver processes. In this article, we aimed to describe different forms of hepatic iron overload (diffuse, heterogeneous, multinodular, focal, hypersiderosis, segmental, intralesional, and periportal) and hepatic iron sparing (focal geographic and nodular and periportal) (Table).

Techniques for evaluation of hepatic iron overload

Ultrasonography
Ultrasonography is not a suitable technique for evaluation of hepatic iron overload, as it cannot detect iron deposition (5). However, nonspecific long-term changes caused by hepatic iron overload like cirrhosis, portal hypertension, or hepatocellular carcinoma can be detected by ultrasound.

Computed tomography
Iron overload is presented as increased liver attenuation (72 HU or more) on unenhanced computed tomography (CT) images due to increased absorption of X-rays by iron (6). Associated hepatic steatosis, which is characterized as decreased attenuation on CT may potentially reduce sensitivity, whereas other factors increasing attenuation of hepatic parenchyma like gold storage in liver (7) and amiodarone administration (8) decrease the specificity of this technique. Therefore, CT is not a reliable technique for diagnosis and quantification of iron overload in the liver. However, CT may be of use in some patients unsuited for MRI, or to differentiate high iron content from calcifications, air, or foreign materials such as surgical clips.

Magnetic resonance imaging
Iron causes a local distortion in the magnetic field and results in T1, T2, and T2* shortening. This effect causes signal loss on T2-weighted spin-echo/fast spin-echo and T2*-weighted gradient echo images, and is used for measurement of iron concentration. Iron-induced T2* shortening...
ing is superior to iron-induced T2 shortening, therefore T2*-weighted images have greater sensitivity to detect iron (9), and are more commonly used for this purpose. It is important to be alert to detect iron overload in the liver, as it is not always clinically evident. In routine abdominal MRI protocols, in-and out-of-phase images, which are generally used for detection of fat, are also helpful in detection of iron. Iron causes signal drop on standard in-phase images, contrary to signal drop effect of fat on out-of-phase. With this principle, many iron quantification methods by MRI depends on gradient echo sequences with T2* weighting, which were acquired with progressively longer echo times.

There are two major methods in quantification of hepatic iron overload, namely, signal intensity ratio methods and relaxometry methods. Signal intensity ratio methods measure the signal intensity of the liver and another tissue or noise and give proportion of these to quantify the liver iron (10, 11), whereas relaxometry methods measure signal intensity of the liver across multiple echo times and calculate T2 or T2* values depending on the performed sequence (12). T2 or T2* values are inversely related with iron concentration. However, R2 or R2* values (1000/T2 or T2*) are directly related to the iron concentration determined by liver biopsy (13). Calculation of R2* and T2* plays an important role in diagnosing the degree of iron overload for planning the treatment with iron chelating agents. A T2* value below 18 ms is accepted as hepatic iron overload (14). A recent study demonstrated that the R2* cutoff value of 147.1 Hz (T2* value of 6.8 ms) discriminates moderate and severe hepatic iron overload from absent and mild hepatic iron overload (15).

Magnetic field strength of the scanner is important for measuring R2 and R2* values as cardiac and liver R2* values measured on 3.0 T is higher than values measured on 1.5 T scanner (16). Higher field strength may be an advantage in detection of tissues containing low iron and when high image resolution is needed. However, higher field strength is more sensitive to magnetic susceptibility artifact, and heavy iron overload in the tissue may cause problem in detection and quantification of iron (17). The software for calculating R2 and R2* maps is not available on all MRI scanners. Apart from these, MRI is a good alternative to biopsy for both diagnosis and treatment monitoring of hepatic iron overload.

### Main points
- Hepatic iron overload can be diagnosed by in- and out-of-phase sequence and T2* and R2* maps.
- MRI is preferred for detection and quantification of hepatic iron.
- Knowledge of different forms of hepatic iron overload and iron sparing would allow correct diagnosis of atypical lesions in hemosiderosis.
- We describe new forms such as hypersiderosis and periportal iron sparing.

### Hepatic iron overload

Iron homeostasis depends on the balance between daily gains (intestinal absorption, reuse from old erythrocytes) and losses (epithelial desquamation, menstruation). This balance is crucial, because there is no effective way for excretion of iron from the body (18, 19). There are two distinct etiologic causes of iron overload: inherited or primary iron overload and secondary iron overload.

### Table. Different forms of hepatic iron overload and iron sparing

<table>
<thead>
<tr>
<th>Hepatic iron overload</th>
<th>Associated conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse siderosis</td>
<td>Hemosiderosis, hemochromatosis</td>
</tr>
<tr>
<td>Heterogeneous siderosis</td>
<td>Iron chelation treatment</td>
</tr>
<tr>
<td>Focal and segmental siderosis</td>
<td>Infarction</td>
</tr>
<tr>
<td>Hypersiderosis</td>
<td>Hemosiderosis</td>
</tr>
<tr>
<td>Intralesional siderosis</td>
<td>Regenerative nodule, Dysplastic nodule, Hemorrhagic focal liver lesions (hepatic adenoma, hepatocellular carcinoma, choriocarcinoma, melanoma)</td>
</tr>
<tr>
<td>Periportal siderosis</td>
<td>Early hemosiderosis, Iron chelation treatment</td>
</tr>
<tr>
<td>Focal nodular and geographic iron sparing</td>
<td>Hemosiderosis</td>
</tr>
<tr>
<td>Periportal iron sparing</td>
<td>Periportal cavernomatous transformation</td>
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</tbody>
</table>

**Figure 1.** a–d. Diffuse siderosis in a patient with thalassemia major. There is signal drop on in-phase image (a) relative to out-of-phase image (b). R2* measurements on R2* map (c) and colored R2* map (d) demonstrate iron overload in the liver, spleen, and pancreas.
syndromes. Primary iron overload (i.e., hereditary hemochromatosis) is an autosomal recessive disorder in which a defective protein causes increased intestinal absorption of iron from small intestine at 5–10 times the normal rate (20). Secondary iron overload syndromes include iron-loading anemias (i.e., thalassemia, sideroblastic anemia, sickle cell disease, chronic hemolytic anemia, aplastic anemia, pyruvate kinase deficiency), chronic liver diseases (i.e., hepatitis C infection, nonalcoholic fatty liver disease, alcoholic fatty liver disease), and iatrogenic (i.e., red blood cell transfusion, long-term hemodialysis) and miscellaneous causes.

Excess iron primarily accumulates in parenchymal cells, particularly in the liver, pancreas, heart, endocrine glands like thyroid and pituitary, and synovium in primary iron overload. However, in secondary iron overload, iron accumulates in reticuloendothelial system (spleen, Kupffer cells, bone marrow, and lymph nodes). Iron also accumulates in hepatocytes and other parenchymal cells after saturation of reticuloendothelial cells, in secondary iron overload. Detection and quantification of hepatic iron overload is important for both primary and secondary iron overload syndromes. In primary iron overload, liver iron content gives information about the risk for hepatic complications such as fibrosis and cirrhosis (4, 21, 22). In iron-loading anemias, liver iron content provides information about total body iron (23), thus quantification of liver iron content helps to monitor these patients and the treatment (2). Liver biopsy is the current reference standard for detection and quantification of iron overload. There are two main limitations of liver biopsy. First, the invasiveness, for which MRI is a good alternative particularly when repetitive/follow-up measurements are needed for treatment monitoring. Second, the sampling error, for which MRI might even be of benefit to determine the best location for biopsy, since hepatic iron overload can have various distributions, as illustrated in this article (4, 24, 25). Therefore hepatic iron accumulation detection, quantification, and follow-up evaluation after treatment depend on imaging methods, especially MRI as described in the previous section.

Hepatic iron overload can be in the form of diffuse, heterogeneous, segmental, focal, hypersiderosis, intralesional siderosis, and periportal siderosis.

**Diffuse siderosis**

Both primary and secondary iron overload can lead to diffuse hepatic iron overload. However, diffuse siderosis is mostly observed in patients receiving multiple blood transfusions. There is a linear correlation between liver iron concentration and R2* value (1/T2*) (Fig. 1).
In some cases, especially patients on treatment with iron chelating agents, heterogeneous siderosis can be seen on R2* maps as a treatment response (Fig. 2).

**Focal and segmental siderosis**

Focal iron accumulation can be seen in liver due to altered or absent perfusion (Fig. 3). We observed areas of focal siderosis in patients who received chemotherapy. Focal iron deposition can be amorphous nodular in shape. These areas demonstrate focal signal drop on in-phase images compared with out-of-phase images (Fig. 4).

**Hypersiderosis**

Hypersiderosis is seen as an area containing more iron compared with the rest of the liver. Theoretically, hypersiderosis can be seen in areas with third inflow due to aberrant venous drainage. Hypersiderosis appear hyperintense on R2* maps and can be seen in multiple blood transfusions (Fig. 5).

**Intralesional siderosis**

Iron can accumulate in regenerative or dysplastic nodules, which are referred as "siderotic nodules" in cirrhosis, unrelated to systemic or hepatic iron overload. The detection of siderotic nodule with MRI is not challenging, however, discrimination of dysplastic nodules from regenerative nodules is not feasible (33) (Fig. 6). Development of hepatocellular carcinoma (HCC) in a siderotic nodule has been defined as nodule-in-nodule appearance on T2- or T2*-weighted images, consisting of intermediate-high intensity focus in low-signal intensity siderotic nodule (34, 35). Iron presence can also be shown with MRI in hemorrhagic focal liver lesions like HCCs, hepatic adenomas (36), and some metastatic lesions like choriocarcinoma (37) and melanoma (38).

**Periportal siderosis**

Excess iron due to increased intestinal absorption initially accumulates in the periportal vein that decrease portal venous flow result in unequal iron deposition in different segments. Segmental siderosis was defined as segmental hypointensity on MRI and was confirmed by liver biopsy as iron deposition in previous studies (30–32).

Focal iron accumulation can be seen in liver due to altered or absent perfusion (Fig. 3). We observed areas of focal siderosis in patients who received chemotherapy. Focal iron deposition can be amorphous nodular in shape. These areas demonstrate focal signal drop on in-phase images compared with out-of-phase images (Fig. 4).
portal hepatocytes (39). Therefore, periportal siderosis can be observed in early phases of hepatic iron overload or after chelation treatment (Fig. 7).

**Focal hepatic iron sparing in siderotic liver**

Iron sparing refers to areas of liver with less iron than surrounding parenchyma, similar to fat sparing in the liver.

**Focal nodular and geographic iron sparing**

Focal iron sparing can be seen in patients with hepatic iron overload due to hemosiderosis usually in segment 4. Location of focal iron sparing can match with usual areas of focal fat accumulation and focal fat sparing. Signal abnormalities in these areas most likely result from the third inflow from aberrant venous drainage into the liver. Most common aberrant venous drainage occurs from Sappey veins, right gastric vein, and left gastric vein. Focal iron sparing can be geographic or nodular in shape (Figs. 8, 9). Nodular forms may mimic a lesion (40).

Tumor cells of HCCs secondary to hepatic iron overload-induced cirrhosis don’t contain iron (41). In this situation, HCC can also be detected as focal nodular iron sparing.

**Periportal iron sparing**

Periportal fat accumulation has been described before (39), but we could not find a case with periportal iron sparing in the literature. We observed periportal iron sparing in a patient with periportal cavernomatous transformation and hemosiderosis related to myelodysplastic syndrome (Fig. 10). The possible mechanism of periportal sparing is normal perfusion in the vicinity of periportal space and caudate lobe. Hypertrophy of the caudate lobe supports this mechanism. Therefore, after the administration of iron chelating agent deferoxamine, iron was cleared only from the areas with normal perfusion.

**Iron and fat coexistence**

There can be coexisting hepatic iron overload and fat accumulation. In previous studies, it was shown that up to 40% of patients with nonalcoholic fatty liver disease have iron overload (42, 43). On the other hand, coexistence of steatosis in patients with primary iron overload was shown to accelerate liver injury (44). In such circumstances, in- and out-of-phase images can cause diagnostic confusion and both detection and quantification of iron and fat become difficult, especially in conventional MRI. However, quantification of both fat and iron is feasible with recent methods that calculate $R2^*$ and proton density fat fraction, simultaneously (45). This approach can help to clarify coexistence of siderosis and steatosis and confusing patterns of fat and iron accumulation (40) (Fig. 11).

**Conclusion**

There are different forms of iron accumulation and sparing in the liver, which can be a result of normal, variant, or abnormal perfusion changes. Recent MRI techniques for hepatic iron detection and quantification can enable better understanding of hepatic iron overload and iron sparing, and may prevent misdiagnosis of focal signal changes related to varying degrees of iron content in patients with siderosis.

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Figure 9. a, b. Focal nodular iron sparing in a patient with thalassemia major. There is a nodular hypointense area in segment 4 on axial $R2^*$ map (a). We observed a lower $R2^*$ value (200 Hz) in this area compared with the rest of the liver (320 Hz) (b).

Figure 10. a–c. Periportal iron sparing in a patient with periportal cavernomatous transformation and hemosiderosis related to myelodysplastic syndrome. On in-phase image (a) there is a signal drop in liver parenchyma compared with out-of-phase image (b) sparing left periportal area. Postcontrast image (c) demonstrates chronic thrombosis of portal vein.
Conflict of interest disclosure

The authors declared no conflicts of interest.

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